Drugs Against Cancer: Stories of Discovery and the Quest for a Cure

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CHAPTER 16

Addiction to oncogenes: a conceptual basis for cancer therapy.

The idea that cancer cells could become addicted to an oncogene came to mind from observations far removed from anything that cancer researchers ordinarily thought about. It came from observations by Michael Yarmolinsky and coworkers of bacteria that become addicted to viruses infecting them. Curing the infection caused the bacteria to die, because the virus generated both a toxin and an antidote. When the virus was eliminated, the toxin survived longer than the antidote and the bacterial cell died (Lehnherr et al., 1993). It was as if the bacteria had become addicted to their infection. Yarmolinsky (Figure 16.1) may have been the first to apply the epithet "addicted" to a living cell.

As explained in the preceding chapter, cancer is often promoted by abnormal activation of a gene that pushes the cells to keep dividing without the normal constraints. The normal version of the gene (proto-oncogene) that stimulates cell division in a *controlled* fashion sometimes becomes mutated or otherwise altered genetically in a manner that stimulates uncontrolled cell division. The altered gene thus becomes an oncogene: a gene that pushes cells to become cancerous.

A rather far-out notion came to mind that an oncogene-addicted cancer cell might be thought of as analogous to a virus-addicted bacterium. Inhibiting the oncogene in a cancer cell addicted to it might then cause the cell to die. Indeed, drugs that inhibited an oncogene in cancer cells sometimes, not only stoped the cells from dividing, but caused the cancer cells to die. It seemed that cancer cells sometimes became dependent on the function an oncogene. As the cell adapted to being continually stimulated by an uncontrolled oncogene, other change would develop that the cancer cell could tolerate only while the oncogene is functioning.

Yarmolinsky and I had met during a course on mathematical probability at Harvard College, and we were now working in the same cancer research building at NIH. He told me about his remarkable bacteria-virus addiction observations when I stopped at his lab one day to pick him up for our frequent lunch breaks together. Some months later, I attended a lecture by Bernard Weinstein. He and I had come to NCI at the same time and were in the same group of Clinical Associates. At the end of the lecture, I told him about Yarmolinsky's observations and suggested that cancer cells might in somewhat analogous fashion become addicted to their oncogenes. Weinstein then assembled evidence from a variety of previous reports to crystallize the concept of oncogene addiction (Weinstein, 2002) (Weinstein and Joe, 2008) (Figure 16.2).

The virus infecting Yarmolinsky's bacteria produced both a toxin and an antidote. If you cured the infection, the antidote disappeared first and the toxin then killed the host cell. Somewhat analogously, deleterious effects of an abnormally expressed cancer gene, an "oncogene", could be compensated by altered activity of other genes. The cancer cells that had those altered gene activities could survive the over-activity of the oncogene and thrive – provided that the oncogene continued to be overactive. The cell would then be dependent on the high activity of the oncogene. Block the activity of the oncogene, and the cell would die. Why? Because the gene activity changes that are protective when the oncogene is over-active are lethal when the oncogene is blocked. That was the original form of the oncogene addiction concept.

Figure 16.1. Michael Yarmolinsky in 2016.

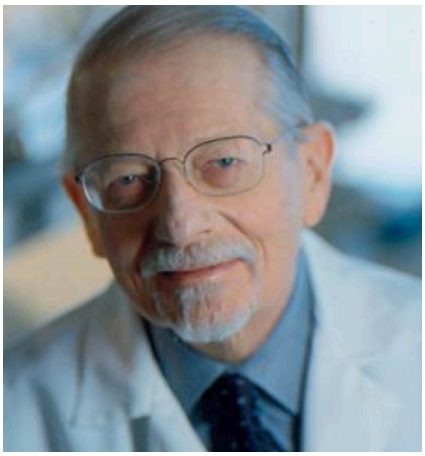

Figure 16.2. I. Bernard Weinstein (1930-2008).

Weinstein's reasoning began by noting a well-established pattern in the way most cancers become malignant: cancer cells develop numerous abnormalities in the amounts of a variety genes that they express, the number of abnormalities increasing as the cells become increasingly malignant (Weinstein, 2002) (Weinstein and Joe, 2008). Many genes become overactive. The essential fact, he reasoned, was that, despite the large number changes, a cancer can sometimes be suppressed by blocking just one of the overactive genes. He argued that cancer cells often become dependent on ("addicted to") a gene (an "oncogene") that drives the cancer process, and that suppressing that oncogene's function with a suitable drug could suppress the cancer. This has become known as "oncogene addiction," analogous to Yarmolinsky's "viral addiction" observation.

In many experiments, switching on an oncogene in a mouse, for example by genetic engineering, caused a malignant tumor to appear. Then, treating the mouse with a drug that suppressed the oncogene caused the tumor to regress. Most of the tumor cells die, but some "differentiate" and assume the guise of normal cells of the kind that initially gave rise to the tumor. In some cases, particularly in tumors of lymphocytes, differentiation into of the tumor cells into seemingly normal lymphocytes was often the main thing that happened. Since lymphocytes normally have a short lifespan, the drug-treated malignant cells that differentiated into normal-seeming lymphocytes tended to be eliminated.

Observations indicating oncogene addiction.

An early experiment indicating oncogene addiction utilized a genetically engineered chronic myelogenous leukemia (CML), a disease discussed in Chapter 14, where a *BCR-ABL* translocation drives the overexpression of the *ABL* oncogene. In 1999, Claudia Huettner, Daniel Tenen and their colleagues at the Harvard Medical School (Huettner et al., 2000) showed that leukemic cells could in fact become addicted to *BCR-ABL*. They induced leukemia in mice by inserting a *BCR-ABL* genetic element into their genome in a manner

that allowed the researchers to control whether or not the inserted *BCR-ABL* was active. When they suppressed the *BCR-ABL*, the leukemia went away. Moreover, when they caused *BCR-ABL* activity to resume, the leukemia came back, only to disappear again when they again suppressed the *BCR-ABL*. That demonstrated that the leukemic cells needed the *BCR-ABL* function in order to survive and proliferate. The leukemic cells had become addicted to the effect that *BCR-ABL* had on them.

Drugs, such as Gleevec, that blocked the overexpressed ABL tyrosine kinas in CML patients, suppressed the disease to such an extent that patients often seemed as if cured. The malignant CML cells had become addicted to the oncogene. When the drug suppressed the ABL tyrosine kinase that was produced by the overactive *ABL* gene, the malignant cells reverted to their normally brief lifespan and died by apoptosis.

However, the disease eventually recurred because the apoptosis required TP53 (see Chapter …) whose gene is the most frequently mutated gene in cancers. The mutation often inactivates the gene, and the CML cells could no longer die by apoptosis. The disease, after remaining dormant for years, could then resumes its malignant course impervious to the drug treatment (Sawyers, 2003).

Another early experiment pointing to oncogene addiction involved the *MYC* oncogene, which is the topic of Chapter 20. Also in 1999, Dean Felsher and Michael Bishop at the University of California San Francisco inserted into mice a *MYC* gene that they (the researchers) could control at will. When *MYC* was active at a high level, it behaved like an oncogene, and the mice developed leukemia. However, when the activity of the gene was stopped, the leukemia went away due to arrest and apoptosis of the leukemia cells. As well as demonstrating oncogene addiction, the experiment showed that the appearance and disappearance of a malignancy could depend on the activity of a single gene (Felsher and Bishop, 1999).

A further example of oncogene addiction was the *HER2* oncogene that is overactive in some types of breast cancer (discussed in Chapter 17). The normal *HER2* gene (the proto-oncogene) becomes overactive due to mutation or gene amplification, which was what made the gene an oncogene. Inhibitors of the overactive HER2 caused those types of breast cancer to shrink. That is part of the EGFR oncogene story related in the next chapter (Chapter 17).

Many additional examples of oncogene addiction were discovered, where a cancer driven by an oncogene is largely, albeit temporarily, eliminated by a drug that suppresses the oncogene's activity (Weinstein and Joe, 2008). Important examples were the *RAS* oncogene (discussed in Chapter 18) and the *MYC* oncogene (discussed in Chapter 20).

Synthetic lethality, a logic-based therapy.

An ideal cancer therapy would be a drug that kills cancer cells but spares the cells of normal tissues. In 2005, Bill Kaelin at the Howard Hughes Institute and Harvard University described situations where that ideal might be achieved (Kaelin, 2005). Called "synthetic lethality," it is where two genes, let's call them A and B, determine whether a cell lives or dies. If both A and B are inactivated, then the cell dies. However, if either or both of them are active, then the cell survives.

How does that relate to cancer therapy? Well, it happens, first of all, when the cancer has a mutation that inactivates a gene – like the above gene A or B. Let's say that the mutation inactivates the cancer's gene A. Then a drug that inactivates gene B would kill the cancer cells, while normal cells would be protected by their non-mutated gene A.

That is, by the way, akin to the cancer cells becoming addicted to gene B, because they can't survive without it. Might it actually be a major way that oncogene addiction works?

So, how was synthetic lethality discovered to exist in cancer and how effective were drugs designed to kill the cancer selectively? Furthermore, how often and in which cancers does a synthetic lethality situation exist that would allow this logic-based therapy?

Although one might think that instances of therapeutically useful synthetic lethality would not be difficult to find, great effort has so far led to only one. That one instance, based on combined inhibition of the BRCA and PARP genes, however has proved very effective and is the topic of Chapter 21.

References

Felsher, D.W., and Bishop, J.M. (1999). Reversible tumorigenesis by MYC in hematopoietic lineages. Mol Cell *4*, 199-207.

Huettner, C.S., Zhang, P., Van Etten, R.A., and Tenen, D.G. (2000). Reversibility of acute B-cell leukaemia induced by BCR-ABL1. Nat Genet *24*, 57-60.

Kaelin, W.G., Jr. (2005). The concept of synthetic lethality in the context of anticancer therapy. Nature reviews Cancer *5*, 689-698.

Lehnherr, H., Maguin, E., Jafri, S., and Yarmolinsky, M.B. (1993). Plasmid addiction genes of bacteriophage P1: doc, which causes cell death on curing of prophage, and phd, which prevents host death when prophage is retained. Journal of molecular biology *233*, 414-428.

Sawyers, C.L. (2003). Opportunities and challenges in the development of kinase inhibitor therapy for cancer. Genes Dev *17*, 2998-3010.

Weinstein, I.B. (2002). Cancer. Addiction to oncogenes--the Achilles heal of cancer. Science *297*, 63-64.

Weinstein, I.B., and Joe, A. (2008). Oncogene addiction. Cancer research *68*, 3077-3080; discussion 3080.